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(54) Title: **HYDROGENOUS MEDICATION**

(57) Abstract: [*As given on the original in English, repeated here for convenience; the more commonly used English term "medication" is preferred to the word "medicament" used in the original patent*] The invention concerns hydrogenous mixtures, which are suitable for preparing medications for treating inflammatory processes in humans and mammals, in particular for treating inflammatory processes in the lungs. Deuterium-containing gas mixtures are used for treating cancer. In addition to hydrogen, the hydrogenous mixtures can contain a pharmacologically active gas, such as nitric oxide, carbon monoxide, nitrous oxide, acetylene or ethylene. The hydrogenous medication is used as an inhalant gas in the form of suppositories, ointments, solutions, dispersions, emulsions, microdroplets, microbubbles, liposomes, microparticles, aerosols, foams, particulate agents, pills, pastilles, capsules, microcapsules, chewing gum, in carriers or as part of a plaster.

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HYDROGENOUS MEDICATION

The invention relates to hydrogenous medications, and procedures for their manufacture and use in the treatment of lung diseases and inflammatory processes in the bodies of mammals and humans.

The use of nitric oxide (NO)-containing gas mixtures in the treatment of reversible pulmonary vasoconstriction and bronchoconstriction is described in WO 92/10228-A1. The NO gas mixture is added to an inhalant gas.

Gases such as nitrous oxide (N_2O) and xenon are used as anesthetics in the field of medicine.

The use of hydrogen gas as a medication is not known in the prior art.

The aim of the invention to prepare a medication for the treatment of inflammatory processes in the body.

It was serendipitously discovered that administration of hydrogenous gas-containing mixtures prevented injury to the lungs in mammals. A general inflammation-inhibiting or anti-inflammatory action of hydrogenous gas-containing mixtures was also observed.

The object of the invention therefore is a medication that contains hydrogen gas or a source of hydrogen gas. The medication contributes to the treatment of mammals and humans.

The term hydrogen (H) should be understood in a general way, and includes all isotopes of hydrogen, i.e., protium (P or ^1H), deuterium (D or ^2H) and tritium (T or ^3H). Molecular hydrogen therefore includes all possible combinations of the hydrogen isotopes – P_2, PD, PT, DT, D_2 and T_2.

Hydrogen gas normally contains molecular hydrogen. Hydrogen gas consists for example of P_2, PD or D_2 or mixtures such as P_2/PD, PD/D_2, P_2/D_2, P_2/PD/ D_2, where the standard hydrogen gas (H_2) contains more than 99% by vol. of P_2. Hydrogen gas may also contain atomic hydrogen (hydrogen in the process of development). Molecular hydrogen exists in two forms: ortho-hydrogen (with parallel-oriented nuclear spin) and para-hydrogen (with antiparallel-oriented nuclear spin). Both forms coexist in thermal equilibrium. At temperatures above 200K a mixture of constant composition with 75% by vol. ortho-hydrogen and 25% by vol. para-hydrogen. appears. Hydrogen gas with this composition is called n hydrogen.

The content data (e.g. vol. %), volume data and pressure data are referenced to normal conditions (20°C, 1.013 bar). The unit ppm is defined as one part by volume per 10^6 parts by volume. The term "hydrogenous gas-containing mixture" also includes pure hydrogen gas.

Hydrogen gas is available on the market in steel tanks at a pressure below 200 bar, for example, or is stored in liquid form (cryogen) at -253°C in ultra-insulated containers.

The medication according to the invention can be used in a variety of forms. The medication may be a hydrogenous gas-containing mixture, or a liquid preparation (e.g. hydrogenous gas-containing mixture or pure hydrogen gas dispersed in a fat emulsion), or a solid preparation (e.g., a gas stored in a clathrate).

Liquid medications are preferably administered either intravenously for systemic use or topically. Solid medications or medications containing solids are preferably applied topically (on the body surface). The gas mixture may consist, for example, of one or more inert gases and hydrogen, or of one or more inert gases, oxygen and hydrogen. Inert gases are nitrogen and the noble

gases such as helium, neon, argon, krypton, xenon and radon.

Gaseous medications are preferably administered for inhalation. In the case of gaseous medications, the medication is either an inhalable gas mixture, e.g. a hydrogen gas mixture with 15% to 30% by vol. oxygen, or the medication may be mixed with the inhalation (respiratory) gas, as described for example in EP 0621 051-A2, to which reference is made. An inhalable medication is produced, for example, by mixing a hydrogen gas-containing mixture, e.g., hydrogen gas in an inert gas, with air or with an inhalant gas. An inhalable medication also that contains hydrogen gas or a source for hydrogen gas is, for example, an aerosol.

The medication, or a precursor for production of the medication, contains hydrogen gas in a pharmacologically active amount. A pharmacologically active amount of hydrogen gas in a gas mixture generally lies in the range of 1 ppm to 100% by vol., preferably in the range of 100 ppm to 80% by vol., more preferably in the range of 0.1% by vol. to 4% by vol., and most preferably in the range of 1 – 4% by vol. hydrogen gas. The administration time for hydrogen gas, highly purified gas or gas mixture, or a hydrogenous gas-containing medication can be either short (e.g., involving seconds, minutes or hours) or extended (e.g., involving several days, or even weeks).

Pure hydrogen gas can be used in the production of the medication. Hydrogenous gas mixtures are preferably used in the production of the medication for reasons of safety or to simplify dosage measurement. A suitable gas mixture for the production of the medication is, for example, a hydrogen/inert gas mixture, e.g., 0.1 – 10% by vol. hydrogen in nitrogen. It is recommended, in the production of hydrogenous gas mixtures or medications, to use gases of very elevated purity (e.g. hydrogen gas or nitrogen gas with a purity of 6.0 or higher).

Parent gases, hydrogenous gas mixtures or gaseous medications are usually compressed and stored in compressed gas containers. Storage of a hydrogenous gas mixture in a compressed gas container is advantageous to the extent that dosage is thereby enhanced. The hydrogen for a hydrogenous gas mixture may also be produced or prepared through electrolysis.

The action of hydrogen gas is not limited to the gas phase. In accordance with Henry's law, a certain portion of hydrogen gas is physically dissolved in liquids. As a result, hydrogen gas is active also in aqueous solutions (e.g. bodily fluids).

In addition, hydrogen gas can be conditionally active in lipophilic media because of its solubility. Dissolved hydrogen gas demonstrates its medicinal effect, for example, in and on the membranes of biological systems, including both cytoplasmic membranes and those of the endoplasmic reticulum, Golgi complex, lysosomes, nuclear membrane and the mitochondria. This is all the more important in that decisive biological reactions occur in such membrane systems, which are distinguished, *inter alia,* by their structured character.

Besides the basic possibility that the medication according to the invention already contains hydrogen gas in gaseous form, the medication may also contain a source for hydrogen gas. Hydrogen exists in chemically or physically bound form in hydrogen gas sources, from which hydrogen gas is released at the selected point in time (e.g. hydrogen-cleaving compounds, metal hydride, clathrathes, microparticles).

Hydrogenous gas-containing medications contribute to the treatment of inflammatory processes in the body, for example organ inflammation (e.g. lungs) or inflammation of the skin or mucosa. Hydrogenous gas-containing medications are especially appropriate for the treatment of inflammatory processes in the lungs, which usually involves all

those processes that trigger a vasoconstrictive or bronchoconstrictive response. Hydrogenous gas-containing medications, especially inhalable hydrogenous gas-containing medications, are suitable for treatment and prevention of the following diseases: ARDS (Adult Respiratory Distress Syndrome), bronchial asthma, COPD (Chronic Obstructive Pulmonary Disease), bronchitis, pneumonia, pulmonary trauma, hypoxia-mediated vasoconstriction.

Without being restricted to this observation, at the current state of knowledge the pharmacological action of hydrogen gas under physiological conditions appears to be based among other things on the fact that an elevated diffusion of reactive species such as radicals (peroxonitrite, hydroxyl radicals) occurs in inflammatory processes, which are captured through reaction with hydrogen. In particular, the reaction of hydrogen gas with endogenous peroxonitrite and hydroxyl radicals appears to be important for the pharmacological action of hydrogen gas.

A toxic action of deuterium-containing gas mixtures on tumor cells has been found serendipitously. Deuterium-containing gas mixtures – i.e., gas mixtures with D, D_2 or PD – can therefore be used to treat tumors or cancer. Deuterium-containing gas mixtures are particularly suitable as an inhalable medication in the treatment or prevention of lung cancer or in supporting the treatment of lung cancer in combination with other medications. For example, in inhalation therapy an inhalant gas with 0.1 – 4% by vol. D_2, PD or their mixture, 20 – 30% by vol. oxygen, and nitrogen as the residual gas can be used. A deuterium-containing gas mixture may also contain H_2. This type of medication combines the beneficial pharmacological effects of a deuterium-containing gas mixture and hydrogen gas. The medication may, for example, be an inhalant gas with 0.1 – 4% by vol. D_2, PD or their mixture, and 0.1 – 4% by vol. H_2, where deuterium-containing gas and hydrogen gas do not exceed a total part of 4% by vol., with 20 – 30% by vol. oxygen, and nitrogen as the residual gas.

For example, an inhalant gas with 10 – 1000 ppm, especially 10 – 100 ppm, D_2, PD or their mixture, can be used in the prevention of lung cancer. A portable device with deuterium-containing gas for mixing with inhalant gas can be used, for example, with heavy smokers. Inhalant gases are usually humidified prior to inspiration.

The appropriate inflammation and explosion limits must be observed in setting the dosage of hydrogen gas in suitable gas mixtures. These limits vary in relation to the degree of oxygen content and the gas humidity, as experts in the field are aware of .

The beneficial pharmacological action of hydrogenous gas mixtures can also be exploited in working with cell, tissue and organ cultures. For example, cell cultures with hydrogenous gas mixtures can be gassed. However, liquid, gel or solid hydrogenous gas-containing preparations or sources for hydrogen gas can be used as components of or additions to the nutrient medium or nutrient solutions for cultures from cells, microorganisms, tissues or organs.

Oxygen uptake in the lungs can be enhanced through treatment with a hydrogenous gas mixture as a medication. Because of the small molecular size of hydrogen and the beneficial transport features associated with this, expressed in lower viscosity and elevated creep and diffusion potential, respiration performance and its concomitant metabolism can be improved, especially in the case of airway obstruction (presence of atelectasis). Without being restricted to this observation, the improved metabolism appears therefore to be related to the fact that oxygen molecules are carried along in the wake of hydrogen molecules.

Breathing can be further improved by addition of helium to the hydrogenous gas mixture. A gas mixture with hydrogen gas, helium and oxygen contributes therefore to the production of an inhalable medication for the treatment of disrupted gas metabolism in the lungs and the treatment of airway obstruction. Such an inhalable medication or respiratory gas contains, for example, 0.1 – 4% by vol. hydrogen, 0.1 – 60% by vol. helium, 20 – 35% by vol. oxygen, and the remainder nitrogen, where all components total 100% by vol., or 0.1 – 4% by vol. hydrogen, 20 – 35% by vol. oxygen, and the remainder helium (total 100% by vol.). To improve metabolism and to treat airway obstruction, hydrogenous gas mixtures are preferably used as medications with a composition of 0.1 – 4% by vol. hydrogen, 1 – 50% by vol. helium, 20 – 30% by vol. oxygen, and the remainder nitrogen (total 100% by vol.), or 0.1 – 4% by vol. hydrogen, 20 – 30% by vol. oxygen, and the remainder helium (total 100% by vol.); and especially 3 – 4% by vol. hydrogen, 10 – 50% by vol. helium, 20 – 30% by vol. oxygen, and the remainder nitrogen (total 100% by vol.), or 3 – 4% by vol. hydrogen, 20 – 30% by vol. oxygen, and the remainder helium (total 100% by vol.).

The hydrogenous gas mixture may contain a pharmacologically active gas, for example NO (nitric oxide), N_2O (nitrous oxide), acetylene (ethine, C_2H_2), ethylene (ethene, C_2H_4) or carbon monoxide (CO). The concentration of pharmacologically active gas can range from 1 ppm to 99% by vol., preferably from 1 ppm to 80% by vol., and most preferably from 1 ppm to 50% by vol. For gaseous medications destined for use as inhalants, the concentration of NO or CO ranges generally from 1 – 1000 ppm, preferably from 1 – 500 ppm,, and most preferably from 50 – 400 ppm. N_2O, ethylene and acetylene can, for example, be contained in concentrations that range from 1 ppm to 80% by vol.,

preferably from 1 ppm to 50% by vol., and most preferably from 1 ppm to 2.5% by vol. in medications destined for inhalation.

It has been serendipitously found that gas mixtures of hydrogen gas and NO are not only advantageously enhanced in their action, but that the action of NO is also increased in the inhalation therapy of lung diseases. NO is therefore particularly preferred as a pharmacologically active gas for addition to a hydrogenous gas mixture. The pharmacological action of NO, which is also found endogenously, is described in "Nüssler A.K.: PZ, No. 2, Vol. 141, Published 1-11-1996, pp. 11-20," to which reference is made. The NO used originated generally from a gas mixture as a source of NO, which is available on the market in compressed gas tanks, for example as a mixture of 900 ppm NO in nitrogen (for medical use).

Substances that give off NO (NO donors) are also suitable as NO sources, e.g., S-nitroso-N-acetyl-penicillamine, S-nitroso-cysteine, sodium prusside, nitroguanidine, glycerol trinitrate, isoamyl nitrate, inorganic nitrite, azide and hydroxylamine.

Hydrogenous gas mixtures with NO or a NO source contribute to the production of a medication for the treatment of reversible and irreversible pulmonary vasoconstriction (pulmonary vessel spasm), bronchoconstriction (spasm-like narrowing of the bronchi) and inflammatory processes in the lungs, in particular for the treatment or prevention of the diseases pneumonia (lung inflammation), pulmonary trauma, bronchial asthma, ARDS (Acute Respiratory Distress Syndrome), PPHN (Persistent Pulmonary Hypertension of the Newborn), COPD (Chronic Obstructive Pulmonary Disease), bronchitis (bronchial inflammation), hypoxia-mediated vasoconstriction (vascular spasm secondary to oxygen deficiency), fat embolus in the lung (obstruction of pulmonary arteries), acute pulmonary edema (acute accumulation of fluid in the lung), acute

mountain sickness, postcardiac surgery acute pulmonary hypertension, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reaction, sepsis, status asthmaticus, hypoxia, chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic pulmonary hypertension or primary pulmonary hypertension, chronic hypoxia.

Instead of the concurrent administration of hydrogen gas and NO in a gas mixture during inhalation therapy, separate administration of hydrogen gas and NO may be advantageous. For example, a hydrogenous gas-containing gas and a NO-containing gas may be added independently of each other to an inhalant gas, which may enable therapeutically suitable doses of each gas [to be delivered] over the course of the treatment. Depending on the systemic response of the patient, the amount of hydrogen gas and of NO in the inhalant gas can therefore be varied.

With regard to the combined administration of a hydrogenous gas mixture and a NO-containing gas or an inhalable NO source, basically all combinations are usable. So, for example, NO may first be added to the inhalant gas, and only then the hydrogen gas, or conversely.

The terms used below: "hydrogenous gas mixtures" or "hydrogenous gas-containing" should be understood to mean mixtures or compounds that contain hydrogen gas (pure or

in mixture), hydrogen gas and NO, or hydrogen gas and a pharmaceutically active gas.

In the production of liquid pharmaceutical compounds (medications), the hydrogenous gas mixture can be dissolved or dispersed in an aqueous phase under atmospheric pressure or applied pressure. The aqueous phase can contain sugar, sugar alcohol, dextrose, dextrane, polysaccharides, (e.g., starch, cellulose, amylose, pectin, agar), derivative polysaccharides (e.g., methylcellulose), proteins (e.g. albumin), surfactants and/or salts. Aqueous gas-containing compounds are described in EP 0122624-A1 and EP0123235-A1, to which reference is made. The viscosity of the aqueous phase can be set through additives (e.g., polyethylene glycol, methylcellulose, etc.). The aqueous phase is preferably suited to infusion and meets physiological conditions (isotonic solutions). Aqueous compounds with carbohydrates (e.g., sugar, polysaccharides) and/or protein or protein mixtures (e.g. albumin) can also be used in the production of hydrogenous gas-containing microbubbles. The production of hydrogenous gas-containing microbubbles is described in WO 96/38181-A1, to which reference is made. Aqueous compounds with hydrogenous gas-containing microbubbles may be obtained, for example, from ultrasound treatment of a solution with 1 part of aqueous solution with 5% by weight human serum albumin and 3 parts of 5% by weight dextrose in an hydrogenous gas-containing environment. The gas-containing microbubbles usually have a diameter of 1 – 10 microns.

The production of gas-containing microdroplets is described in US 4622219, to which reference is made.

Liquid or gel pharmaceutical compounds may also be produced by utilizing the fact that the hydrogenous gas mixture is dissolved or dispersed in a lipophilic phase under atmospheric pressure, or preferably under applied pressure.

In terms of lipophilic components, the lipophilic phase contains alkan or an alkan mixture (e.g., heptane, higher alkanes, mineral oil), plant or animal oils (e.g., olive oil, cotton seed oil, soybean oil, thistle oil, fish oil), ethers (e.g., dipropyl ether, dibutyl ether), esters (e.g., long-chain ester or hydrophobic ester), silicones, fluorocarbon compounds (e.g., perfluoropolyether, perfluorodecaline, perfluorotriptopylamine, perfluoromethyl adamantane, blood substitute materials, perfluorobromalkyl ether, perfluorohexyl ether, perfluorobutyl ether, perfluoroalkylaryl alkene, perfluoroaryl ether, perfluoroaryl alkene), one or more lipids (e.g. hydrocarbons such as tricontane, squalene, carotinoids; alcohols such as wax alcohols, retinol, cholesterine; ether; carbonic acids such as fatty acids; ester (neutral fats, mono-, di-, tri-acylglycerine, waxes, stearic acid ester); amide (ceramide); glycolipids or phospholipids (e.g., phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl glycerol, phosphatidyl inositol, lecithin). The lipophilic phase may in particular contain liposomes or consist of liposomes. The lipophilic phase preferably contains a surfactant. The lipophilic hydrogenous gas-containing phase can be used directly as a medication or can be mixed with a hydrophilic phase (to form a dispersion, emulsion or suspension). The hydrophilic phase can contain water and/or a hydrophilic solvent such as ethanol, glycerol or polyethylene glycol. An emulsion preferably contains one or more surfactants and/or one or more emulsifiers. Suitable emulsifiers are, for example, soy phosphatide, gelatin or protein phosphatide. The emulsions or suspensions contain, for example, 10 – 30% by weight lipophilic phase. Suitable fatty emulsions are commercially available. For example, the Pharmacia & Upjohn company, Erlangen, markets the products Intralipid® 10 (100 g soybean oil, 6 g phosphatidyl choline, 22 g glycerol in 1000 mL water) and Intralipid® 20 (200 g soybean oil, 12 g phosphatidyl choline, 22 g glycerol in 1000 mL water).

Mixtures from lipophilic and hydrophilic phases (e.g. fatty emulsion) are fed gas by conducting or bubbling the gas, for example, through the mixture under atmospheric pressure or applied pressure (e.g., 1 – 300 bar) at a temperature of, for example, 0 – 50°C. Preferably, the hydrogenous gas-containing mixture is produced in high-pressure autoclaves by commingling the mixture and gas at a pressure of 100 – 300 bar. But it is also possible to load the lipophilic phase with a hydrogenous gas-containing mixture first, followed by the mixture from the hydrophilic phase.

Liquid or gel pharmaceutical compounds can be hydrogenous gas-containing liposomes or hydrogenous gas-containing, liposome-containing liquids. Hydrogenous gas-containing liposomes can be produced by conventional methods. The production of gas-containing liposomes is described in US 5334381, to which reference is made. The pharmaceutical compounds with hydrogenous gas-containing liposomes are generally used as injectable medications. Ointments with hydrogenous gas-containing liposomes can also be produced. The ointments are applied externally, for example.

Conventional methods such as ultrasound treatment or mechanical homogenization can be used in the production of hydrogenous gas-containing solutions or emulsions, in particular liposomes. For example, the Ultra-Turrax® from the Jahnke & Kunkel company can be used as a homogenization device. Liquid hydrogenous gas-containing compounds can also be produced by bubbling the liquid (e.g., through fine particle sinters in a gas-washing bottle). Loading with hydrogenous gas-containing gas is preferably performed under pressure.

Liquid or gel pharmaceutical compounds can contain hydrogenous gas-containing microparticles. The microparticles generally have a particle diameter in the range of 0.1 – 40 microns. The microparticles are constructed, for example, of polymers and contain the gas in a polymer capsule.

The polymers are preferably biodegradable. Suitable polymers are, for example, homopolyaldehydes or copolyaldehydes with a molecular weight in the range of 1000 – 12000 dalton. Suitable monomers are, for example, alpha/beta-unsaturated aldehydes such as acrolein and glutaraldehyde. The aldehyde functions (formyl groups) of the microparticles are suitable directly or after conversion to other functional groups (e.g., hydroxy or carboxyl groups) for derivatization with very varied coupling agents, e.g., hydroxyl amine, trihydroxymethyl aminomethane, 3-amino-1-propane sulfonic acid, D-glucosamine hydrochloride, amino mannitol, urea, human serum albumin, hydrazine, peptides, proteins, polyglycol amines, amino polyalcohols, (e.g., HO-PEG-NH_2 or NH_2-PEG- NH_2; PEG = polyethylene glycol) or acid group-containing compounds (e.g., PEG-coupling -glutamic acid, PEG- coupling -DTPA, or PEG- coupling -EDTA; PEG = polyethylene glycol). PEG groups usually have a molecular weight under 100000 dalton, preferably under 40000 dalton. The production and formulation of gas-containing microparticles is described in EP 0 441 468-B1, to which reference is made. Hydrogenous gas-containing microparticles can be used in a variety of medicinal formulations (e.g., 50 mg hydrogenous gas-containing microparticles, 860 mg sodium chloride in 100 mL water). Pharmaceutical compounds contain, for example, 0.1 µg – 100 mg microparticles per mL, preferably 10 µg – 10 mg microparticles per mL.

Gas cavitates or clathrates are used as ultrasound contrast media. Their production is described in EP 0 357 163-A1, to which reference is made. Pharmaceutical compounds with cavitates or clathrates of hydrogenous gas mixtures consist, for example, of hydroquinone, urea or thiourea as the so-called host molecule (host substance) and the hydrogen gas as the guest molecule. The production of clathrates is generally performed using solutions of the host substance in a solvent such as ethanol or propanol, where the heated solution (e.g., 60°C, 70°C or higher, depending on the host substance) is introduced into a high-pressure autoclave and the solution is impinged on the hydrogenous gas at high pressure (e.g., 150–300 bar).

The high-pressure autoclave is usually then maintained at a set temperature for some time (e.g., 80°C for 2 hours). Next, the high-pressure autoclave is gradually cooled (e.g. over 5 days). The precipitated crystals are then separated and usually washed in the solvent. The nuclear size of the crystal can vary, depending on production conditions or the mechanical processes of particle comminution. The crystalline clathrates may be coated with hydrophilic, lipophilic or amphiphilic adjuvants. For application, the clathrates are placed (e.g. suspended) in a sterile aqueous system with additives to set the. viscosity, surface tension, pH and osmotic pressure. In the case of hydroquinone as a host substance, an aqueous system with the following compound is preferably suitable: 1% gelatin solution, 1% albumin solution, 10% glycerol solution, 15% propylene glycol solution, mixtures of sodium cholate and phosphatidyl choline in water, 0.01–1% phosphatidyl choline dispersion (aqueous), 1% methylcellulose, 1-2% dextrane solution, 1% agar solution, 2% Tween solution (Tween 80) and 1% gum arabic.

Dissolution of the clathrate releases its gas content. Among other factors, the rapidity of release of the gas is dependent on the host substance, nuclear size and the aqueous system employed; it can be set within a wide range of limits. Thus with the help of a clathrate, injectable hydrogenous pharmaceutical preparations can be obtained in a simple manner.

For example, 10 mg of the hydroquinone/H_2 complex (3:1 complex) releases about 0.03 mg H_2.

Hydrogenous gas medications (for example, with or without NO, CO_2, N_2O, acetylene or ethylene) are used, *inter alia*, in the form of suppositories, ointments, solutions, dispersions, emulsions, microdroplets, microbubbles, liposomes, microparticles, aerosols, foams, particulate agents, pills, pastilles, capsules, microcapsules, types of chewing gum and in carriers or as part of a plaster.

Gaseous medications can be applied to the surface (topically), for example with bell-shaped containers with or without using pressure.

Example

Prophylactic hydrogen gas inhalation

The prophylactic action of hydrogen gas in an inhalant gas was investigated in a study on sheep. Artificial ARDS was induced with oleic acid. Standard inhalant gas consists of 50% by vol. oxygen, with the remainder nitrogen. The hydrogenous gas-containing inhalant gas was a gas mixture of 50% by vol. oxygen, 3.6% by vol. hydrogen, and the remainder nitrogen. The inhalant gas was delivered via an inhalation device. The FiO_2 (fraction of inspiratory oxygen) was kept constant at 0.5 (but a stepwise variation of 21 – 100% in the oxygen content is possible).

The animals were catheterized 2 days prior to the experiment – i.e., under anesthetic, a central venous catheter was installed for medication and fluid delivery, as well as for invasive monitoring. The invasive monitoring included cardiac output (a record of the heart's pumping capacity in L/min; abbrev. CO) by means of a Swan-Ganz catheter, which works on the principle of thermodilution; measurement of superior vena caval pressure anterior to the right atrium; measurement of pressure in the pulmonary artery and a peripheral artery. Measurement of fluid content in the lungs was performed by means of a fiber optic probe in the femoral artery (COLD, Pulsion, Munich, Germany).

During the experiment the test animals were first anesthetized with a barbiturate (thiopental) and then an narcotic inhalant (isoflurane). The animals were put on a pressure-controlled ventilator to maintain breathing (Servo SV 900, Siemens, Germany).

The gas mixture of 3.5% by vol. H_2 and the remainder nitrogen (pressure gas tank from Messer Griesheim) was introduced into the respiratory system of the test animals via a so-called disk-type gas mixer, which is normally used for anesthesia with N_2O. It was possible to control for a precise H_2 concentration by using a density conversion factor, as well as externally via the disk-type gas mixer. The H_2 concentration of the inspiratory gas (gas breathed in) and the expiratory gas (gas breathed out) was monitored. Electronic sensor measuring devices (Compur) and heat conduction-based measuring devices (Hydros, Rosemount) were used to measure H_2. Once the fixed value determination was made, the respiration parameters were not adjusted again during the procedure.

The procedure with hydrogenous inhalant gas lasted 60 minutes. Afterwards, ARDS was induced with oleic acid (see: Schuster, Daniel P.:Clinical Lessons from the Oleic Acid Model of Acute Lung Injury, Am. J. Respir. Crit. Care Med., Vol. 149, 1994, pp. 245-260).

The results are summarized in the Table below.

Table:

Measurement results from a sheep undergoing prophylactic hydrogenous gas therapy prior to induction of artificial ARDS, and from a sheep without hydrogenous gas therapy prior to induction of ARDS, compared with the exit values for ARDS in the sheep.

paO2 = partial oxygen pressure

paCO2 = partial carbon dioxide pressure

SaO2 = saturation of oxygen

PAPmean = mean pulmonary artery pressure

CO = cardiac output

Numbers with prefixes are relative deviations, numbers in parentheses are absolute values

Parameter	ARDS – Exit values after oleic acid administration	Sheep with H2 prior therapy and induced ARDS	Sheep without H2 prior therapy and induced ARDS
paO2 / mmHg	(54)	+20 (65)	+12 (60)
paCO2 / mmHg	(48)	-10 (43)	-5 (46)
paO2 / paCO2	(134)	+50 (201)	+35 (187)
SaO2 / %	(78)	+15 (90)	+8 (84)
Lymph flow / mL/h	(32.5)	+18 (34)	+20 (39)
Lung fluid / mL/kg	(15)	-6 (14)	+/- 0 (15)
PAPmean / mmHg	(15)	+5 (14)	-8 (14)
CO / L/min	(4.5)	+3 (4.6)	-15 (3.8)

On the basis of the results from the table, the hydrogen gas therapy can be considered to have a protective effect in cases of direct injury to the lung. The administration of oleic acid leads to the release of oxygen radicals through activation of various inflammatory mediators, and this in turn induces toxic injury in the pulmonary tissue .

This damage to the cell barrier precipitates an increased accumulation of fluid in the interstitial and alveolar tissue of the lung, which leads to severe gas metabolism disturbance. The test results indicate that hydrogenous gas therapy produces a reduction in gas metabolism disturbance, and an increase in lymph flow, as well as a decrease in lung fluid, which benefits the cell barrier.

Claims

1. Medication containing hydrogen gas or a source for hydrogen gas.

2. Medication according to Claim 1, characterized in that it exists as a gas, liquid, gel or solid.

3. Medication according to Claim 1 or 2, characterized in that the hydrogen gas contains one or more of the hydrogen isotopes protium, deuterium or tritium.

4. Medication according to Claims 1 through 3, characterized in that it contains nitric oxide, carbon monoxide, nitrous oxide, acetylene or ethylene.

5. Medication according to Claims 1through 4, characterized in that it contains a hydrogenous gas mixture with 1 ppm (volume percent) to 99% by vol. nitric oxide, carbon monoxide, nitrous oxide, acetylene or ethylene.

6. Medication according to Claims 1 through 5, characterized in that the hydrogenous gas medication is used as an inhalant gas, in the form of suppositories, ointments, solutions, dispersions, emulsions, microdroplets, microbubbles, liposomes, microparticles, aerosols, foams, particulate agents, pills, pastilles, capsules, microcapsules, chewing gum, in carriers or as part of a plaster.

7. Medication according to Claims 1 through 5, characterized in that microdroplets, microbubbles, liposomes, microparticles or clathrates containing hydrogenous gas-containing or hydrogen gas and one or more of the gases nitric oxide, carbon monoxide, nitrous oxide, acetylene or ethylene are contained in the medication.

8. Use of the medications according to Claims 1 through 7, characterized in that the medication is administered locally, intracutaneously or transcutaneously for therapy; intravenously for systemic use; intrarterially orally or rectally through partial exchange of bodily fluid or lymph components; intrapleurally, intrathecally, intraventricularly, intraperitoneally, intracavitarily in an OR environment for use in cavities.

9. Use of a hydrogenous gas-containing compound or gas mixture for the production of a medication for the treatment or prevention of ARDS (Adult Respiratory Distress Syndrome), bronchial asthma, COPD (Chronic Obstructive Pulmonary Disease), bronchitis, pneumonia, pulmonary trauma, hypoxia-mediated vasoconstriction and for the treatment of airway obstruction (atelectasis) or inflammatory processes.

10. Use of a hydrogenous gas-containing and a nitric oxide-containing compound or gas mixture for the production of a medication for the treatment or prevention of pulmonary vasoconstriction, bronchoconstriction or airway obstruction.

11. Use of a hydrogenous gas-containing and a nitric oxide-containing compound for the production of a medication for the treatment of reversible and irreversible pulmonary vasoconstriction (pulmonary vessel spasm), bronchoconstriction (spasm-like narrowing of the bronchi) and inflammatory processes in the lungs.

12. Use of a hydrogenous gas-containing and a nitric oxide-containing compound or gas mixture for the production of a medication for the treatment or prevention of the diseases pneumonia (lung inflammation), pulmonary trauma, bronchial asthma, ARDS (Acute Respiratory Distress Syndrome), PPHN (Persistent Pulmonary

Hypertension of the Newborn), COPD (Chronic Obstructive Pulmonary Disease), bronchitis (bronchial inflammation), hypoxia-mediated vasoconstriction (vascular spasm secondary to oxygen deficiency), fat embolus in the lung (obstruction of pulmonary arteries), acute pulmonary edema (acute accumulation of fluid in the lung), acute mountain sickness, postcardiac surgery acute pulmonary hypertension, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reaction, sepsis, status asthmaticus, hypoxia, chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic pulmonary hypertension or primary pulmonary hypertension, chronic hypoxia.

13. Use of a deuterium-containing gas mixture for the production of a medication for the treatment or prevention of cancer.

14. Use of a deuterium-containing gas mixture for the production of a medication for the treatment or prevention of lung cancer.

15. Use of a hydrogenous gas mixture or a hydrogenous gas compound in cell cultures, tissue cultures, organ cultures or microorganism cultures.

16. Use of a hydrogenous gas mixture or a hydrogenous gas compound to reduce the concentration of peroxonitrites or hydroxyl radicals in biological material.

17. Use of a hydrogenous gas mixture or a hydrogenous gas compound for the production of a medication to reduce the concentration of peroxonitrites or hydroxyl radicals in the bodies of mammals or humans.

18. Use of a gas mixture composed of hydrogen gas, helium and oxygen gas for the production of an inhalable medication in the treatment of gas metabolism disturbance in the lungs and the treatment of airway obstruction.

19. Use of a liquid containing carbohydrates, lipids, peptides or proteins for the production of a hydrogenous gas medication.

Attachments:

[Separately available in English and German]

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